PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION** See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP 03/12206	International filing date *(day/month/year)* 27.10.2003	Priority date *(day/month/year)* 11.11.2002
International Patent Classification (IPC) or both national classification and IPC C12P7/62		
Applicant UNILEVER PLC et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13.05.2004	02.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Lejeune, R Telephone No. +31 70 340-2347

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/12206

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1, 2, 5-22	as originally filed
3, 4	filed with telefax on 14.02.2005

Claims, Numbers

1-7	received on 13.12.2004 with letter of 13.12.2004
8-13	filed with telefax on 14.02.2005

Drawings, Sheets

1/3-3/3	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 12,13

   because:

   ☒ the said international application, or the said claims Nos. 12,13 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-13
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations

see separate sheet

III. No opinion (Continuation)

For the assessment of the present claims 12, 13 the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 12 and 13 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

V. Reasoned statement (Continuation)

Reference is made to the following documents:

D1: MAUGARD THIERRY ET AL. JOURNAL OF MOLECULAR CATALYSIS B ENZYMATIC, vol. 8, no. 4-6, pages 275-280

D2: O'CONNOR C J ET AL. AUSTRALIAN JOURNAL OF CHEMISTRY, vol. 45, no. 4, 1992, pages 641-649

D3: AJIMA A ET AL. BIOTECHNOLOGY LETTERS, vol. 8, no. 8, 1986, pages 547-552

D4: WO 01/078676

The application deals with the enzymatic (trans)esterification of retinol (or retinyl esters) in animal or vegetal fat, in solvent free conditions.

NOVELTY (Art. 33(2) PCT)

The subject matter of claims 1-7 is new, since enzymatic production of retinyl esters in the presence of animal or vegetable fat or oil is not disclosed in the prior art.

The subject matter of claims 8-13 is new because the prior art (D1, D2, D3, D4) does not disclose mixtures of retinyl esters of fatty acids wherein the mixture reflects the composition of the fat or oil from which it was prepared.

INVENTIVE STEP (Art. 33(3) PCT)

The subject matter of claims 1-13 does involve an inventive step because although the prior art discloses the enzymatic esterification of retinol with fatty acids (palmitate and oleate, D1-D3), there is no indication to use animal or vegetable fats/oils as fatty acid sources.

that a solvent is necessary for the reaction to be carried out, and does not discuss the nature or source of the acyl donor.

The present invention aims to provide a new method of preparing retinyl esters for use e.g. in topical cosmetic compositions, which esters may have various benefits associated with them over prior art teachings, including being simpler and cheaper to produce, without the requirement for organic solvents or significant down-stream processing. Surprisingly the products of the invention also show much enhanced stability, and reduced irritancy on the skin.

Thus, according to a first aspect of the invention, there is provided a method of producing a retinyl ester comprising subjecting a composition comprising retinol or a retinyl ester and a fat or oil of animal, vegetable or algal origin to enzyme catalysed trans-esterification in solvent free conditions to produce a retinyl ester.

In a further aspect, there is provided a mixture of retinyl esters of fatty acids prepared by the method described above, wherein the mixture reflects the composition of the fat or oil from which it was prepared. Preferably the mixture also comprises the fat or oil.

Preferably at least one ester comprises a conjugated or nonconjugated C18:3 or C18:4 retinol fatty acid ester.

According to yet a further aspect there is provided a topical composition for application to human skin containing a mixture of retinyl esters or a composition containing a retinyl ester prepared as described above.

According to yet a further aspect there is provided a cosmetic method of treating human skin comprising applying thereto a topical composition as described above.

The method may be used to provide compositions containing a fat or oil of animal, vegetable or algal origin, and which contain (or from which may be isolated) retinyl esters with fatty acid portions which reflect the fatty acid composition of that animal, vegetable or algal fat or oil. For example, when produced in sunflower oil, the method produces sunflower fatty acid retinyl esters from the enzyme catalysed trans-esterification of sunflower oil. The resultant retinyl esters are predominantly the linoleic and oleic forms, reflecting the fatty acid composition of the sunflower oil.

The method can be extended to the use of any fat or oil of animal, vegetable or algal origin.

As a result, the method can be used to synthesise retinyl esters containing fatty acids having C_{12-22} chain lengths,

8. A mixture of retinyl esters of fatty acids prepared according to the method of any of claims 1 to 7, wherein the mixture reflects the composition of the fat or oil from which it was prepared.

9. A mixture of retinyl esters of fatty acids according to claim 8 further comprising the fat or oil.

10. A mixture of retinyl esters according to claims 8 or 9 wherein at least one ester comprises a conjugated or nonconjugated C18:3 or C18:4 retinol fatty acid ester.

11. A topical composition for application to human skin containing a mixture of retinyl esters according to Claims 8 to 10.

12. A cosmetic method of treating human skin comprising applying thereto a topical composition according to claim 11.

13. A method of providing at least one skin care benefit selected from: treating/preventing wrinkling, sagging, aged and/or photodamaged skin; boasting collagen deposition on skin, boosting decorin production in skin; soothing irritated, red and/or sensitive skin; improving skin texture, smoothness and/or firmness; providing anti-inflammatory benefits; enhancing skin differentiation; reducing sebum production; or the prevention or treatment of acne; comprising applying

thereto a mixture of retinyl esters according to any of claims 8 to 10, or a topical composition according to claim 11.